Postnatal Pancreas of Mice Contains Tripotent Progenitors Capable of Giving Rise to Duct, Acinar, and Endocrine Cells In Vitro.

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Public Summary:
Postnatal pancreas is a potential source for progenitor cells to generate endocrine beta-cells for treating type 1 diabetes. However, it remains unclear whether young (1-week-old) pancreas harbors multipotent progenitors capable of differentiating into duct, acinar, and endocrine cells. Laminin is an extracellular matrix (ECM) protein important for beta-cells' survival and function. We established an artificial extracellular matrix (aECM) protein that contains the functional IKVAV (Ile-Lys-Val-Ala-Val) sequence derived from laminin (designated aECM-lam). Whether IKVAV is necessary for endocrine differentiation in vitro is unknown. To answer these questions, we cultured single cells from 1-week-old pancreas in semi-solid media supplemented with aECM-lam, aECM-scr (which contains a scrambled sequence instead of IKVAV), or Matrigel. We found that colonies were generated in all materials. Individual colonies were examined by microfluidic reverse transcription-polymerase chain reaction, immunostaining, and electron microscopy analyses. The majority of the colonies expressed markers for endocrine, acinar, and ductal lineages, demonstrating tri-lineage potential of individual colony-forming progenitors. Colonies grown in aECM-lam expressed higher levels of endocrine markers Insulin1, Insulin2, and Glucagon compared with those grown in aECM-scr and Matrigel, indicating that the IKVAV sequence enhances endocrine differentiation. In contrast, Matrigel was inhibitory for endocrine gene expression. Colonies grown in aECM-lam displayed the hallmarks of functional beta-cells: mature insulin granules and glucose-stimulated insulin secretion. Colony-forming progenitors were enriched in the CD133(high) fraction and among 230 micro-manipulated single CD133(high) cells, four gave rise to colonies that expressed tri-lineage markers. We conclude that young postnatal pancreas contains multipotent progenitor cells and that aECM-lam promotes differentiation of beta-like cells in vitro.

Scientific Abstract:
Postnatal pancreas is a potential source for progenitor cells to generate endocrine beta-cells for treating type 1 diabetes. However, it remains unclear whether young (1-week-old) pancreas harbors multipotent progenitors capable of differentiating into duct, acinar, and endocrine cells. Laminin is an extracellular matrix (ECM) protein important for beta-cells' survival and function. We established an artificial extracellular matrix (aECM) protein that contains the functional IKVAV (Ile-Lys-Val-Ala-Val) sequence derived from laminin (designated aECM-lam). Whether IKVAV is necessary for endocrine differentiation in vitro is unknown. To answer these questions, we cultured single cells from 1-week-old pancreas in semi-solid media supplemented with aECM-lam, aECM-scr (which contains a scrambled sequence instead of IKVAV), or Matrigel. We found that colonies were generated in all materials. Individual colonies were examined by microfluidic reverse transcription-polymerase chain reaction, immunostaining, and electron microscopy analyses. The majority of the colonies expressed markers for endocrine, acinar, and ductal lineages, demonstrating tri-lineage potential of individual colony-forming progenitors. Colonies grown in aECM-lam expressed higher levels of endocrine markers Insulin1, Insulin2, and Glucagon compared with those grown in aECM-scr and Matrigel, indicating that the IKVAV sequence enhances endocrine differentiation. In contrast, Matrigel was inhibitory for endocrine gene expression. Colonies grown in aECM-lam displayed the hallmarks of functional beta-cells: mature insulin granules and glucose-stimulated insulin secretion. Colony-forming progenitors were enriched in the CD133(high) fraction and among 230 micro-manipulated single CD133(high) cells, four gave rise to colonies that expressed tri-lineage markers. We conclude that young postnatal pancreas contains multipotent progenitor cells and that aECM-lam promotes differentiation of beta-like cells in vitro.

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